or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Arnold, White & Durkee Deposit Account No. 01-2508/ARCD:086/SER.

The Examiner is requested to enter the following amendments and consider the accompanying remarks.

REMARKS

I. Claims in the Case

Claims 1-36 are currently pending.

II. Rejection of Claims 1-36 Under 35 U.S.C. § 112, First Paragraph

The Action rejects the claims as non-enabled, purportedly because the gene therapy procedures set forth in the specification do not teach radioprotection or the synergistic effect of radiotherapy and a delivered radiosensitizing gene in animals, including humans. Applicants traverse.

The Action cites the Marshall article, among others, to support a proposition that there has been no unambiguous evidence that genetic treatment has produced any therapeutic benefits, and moreover that undue experimentation will be required to use the DNA *in vivo*. Applicant's position is that while some forms of gene therapy may have problems relating to inefficiency, and would require excessive experimentation to optimize, the examples set forth in the present invention demonstrate that such procedures may be utilized in an may be utilized in an *in vivo* setting. Moreover, an article by Crystal, appearing in *Science* 270:404-409 (Exhibit A) emphasizes that

"probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible. ... Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies." *Id.* at 405 (emphasis added). See Table 1 for a summary of studies showing the feasibility of gene transfer to humans. Thus, contrary to the assertions set forth in the Action, gene therapy in both *in vitro* and *in vivo* situations has been successful utilizing viral vectors, liposomal carriers, and direct DNA injection. Importantly, Crystal also shows in Table 2 data from human gene transfer studies in which transfer of genetic material has evoked a biologic response that is relevant to the underlying disease. Included are transfer vectors that are retroviral, adenoviral, and a plasmid-liposome complex.

Having shown that *in vivo* use of the constitutive genetic constructs coupled with treatment of cells with ionizing radiation is enabled, Applicants respectfully request withdrawal of the § 112, First Paragraph rejection.

III. Rejection of Claims 8 and 19 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claims 8 and 19 as indefinite, purportedly because TIL, or tumor infiltrating lymphoctes, are not known in that art as a gene transfer vector. Applicants traverse.

Applicants point out that page 22 of the specification shows the use of TIL, or tumor infiltrating lymphocytes as a gene transfer vector. TIL are also used in the art as gene transfer vehicles, as explained in Exhibit B. This paper by Culver *et al.* shows, for example, that murine helper T cells could express both neomycin-resistance and human

deaminase genes when transfected into cells in culture (FIG. 2; p. 3158). Moreover, these authors showed that exponential cultures of IL-2-stimulated TIL could be efficiently transduced with the neomycin-resistance gene using the retroviral vector N2. Effectiveness of the transfer was shown by subsequent G418 selection (FIG. 3, Table 1).

Applicants submit that the use of TIL as a gene transfer vehicle is shown by, for example, the Culver article, and therefore it is requested that this rejection be withdrawn.

IV. Rejection of Claims Under 35 U.S.C. § 103

Finally, the Action rejects the claims over Applicants PCT application, Neta *et al.*, and the specification. Applicants traverse.

First, the PCT publication is directed primarily to the use of genetic constructs that are radiation-inducible to produce a gene product following such irradiation. The present inventors discovered, however, that certain constitutive promoters that are operatively linked to structural genes are useful in expressing therapeutic proteins within a cell. Moreover, as set forth in the Action, the PCT publication does not specifically disclose the use of gene transfer vectors for radioprotection, and does not specifically disclose HSV-1 and adenovirus and vectors for transfer of radiosensitizing genes. There is no teaching or suggestion that such constructs will be useful for radioprotection, or how they should be administered.

Neta *et al.* simply discusses some proteins that may be useful in radioprotection. Neta does not teach or suggest that the genes for these proteins should be operatively linked to a constitutive promoter and transfected into cells as part of a treatment protocol, either to enhance the radiosensitivity in a target tissue, or to radioprotect certain cells that fall outside the target range. Neta *et al.* is directed primarily to the external application of

pharmacological doses of cytokines to act as radioprotectors, rather than any internal manipulation of cytokine levels. For example, Neta reports that cytokines given as single or multiple injections can accelerate hemopoetic system recovery an survival following radiation exposure (p. 393, second column; see also p.391, p.394).

Applicants' specification simply points out that there are art-recognized gene therapy procedures may be utilized to accomplish the goal of transfecting the constitutive constructs of the present invention into a host cell. See also Exhibit A.

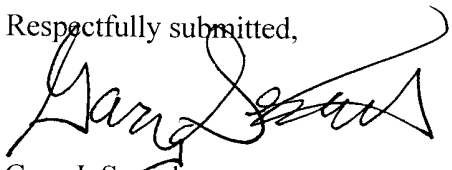
In conclusion, none of the cited publications would have suggested to one of ordinary skill in the art at the time of the invention that he could combine the disparate teachings of the references and obtain the invention as presently claimed. The only suggestion of this combination that Applicants can find is contained in their own application, and it is impermissible to use hindsight to use what only the inventors teach in their application against them. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 30-3, 311 (Fed. Cir. 1983). The cited references only lead to a piecemeal reconstruction of the record, in light of Applicants' disclosure. It is submitted that one cannot pick and choose from any one reference only what will support a given position, to the exclusion of other parts necessary to fully appreciate what the reference fairly suggests to one of skill in the art. *In re Kamm and Young*, 172 USPQ 298, 301-302 (CCPA 1972). The cited combination of Applicants' PCT application, Neta *et al.* and what is purportedly disclosed in the specification does not contain any suggestion to those of ordinary skill that they combine the teaching of the references and create the claimed invention of effecting changes in cells that have been transfected with a genetic construct containing a constitutive promoter operatively linked to a therapeutic gene. The non-

obviousness of the present invention lies in the ability to utilize constitutive promoters, such as the Cmv early gene promoter, to express structural genes for cytokines directly in the cells to radioprotect or radiosensitize the cells prior to treatment with ionizing radiation, such that the target cells receive therapeutic doses of the requisite gene product. This process is neither taught nor suggested by the cited art. Applicants therefore request that this rejection be withdrawn.

V. Conclusion

This is submitted to be a complete response to the Official Action. Applicants submit that in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested. If the Examiner has any questions or comments, a telephone call to the undersigned applicants' representative at (512) 418-3012 is earnestly solicited.

Respectfully submitted,



Gary J. Sertich
Reg. No. 34,430

ARNOLD, WHITE & DURKEE
P.O. Box 4433
Houston, Texas 77210
(512) 320-7200

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